REMARKS

I. Preliminary Remarks

In the Office Action dated September 2, 2004, the Examiner maintained the rejection of claims 1-4, 8, 9, 12, 23, and 26 under 35 U.S.C. § 102(b) as being anticipated by Davis et al., Plant Molecular Biology 6:23-32, 1986 (hereinafter, "Davis"), asserting that Davis teaches that acetic acid or acetate alone is an elicitor of therapeutically useful compounds from plants. Additionally, the Examiner maintained the rejection of claims 1-4, 7-21, 23, 25, and 26 under 35 U.S.C. § 103(a) over Davis in view of Stevens et al. (hereinafter, "Stevens") (assertedly extracting flavonoids from plants), and U.S. Pat. No. 3,810,990 (Jurd et al.; hereinafter, "Jurd") (assertedly assaying therapeutically active flavonoids). Further, the Examiner rejected claims 1-4 and 6-26 under 35 U.S.C. § 103(a) over Davis in view of U.S. Pat. No. 4,871,574 (Yamazaki et al.; hereinafter, "Yamazaki") (assertedly macerating plant material to obtain therapeutics). Claims 1-4 and 6-27 will be pending upon entry of the present amendment; claims 1-4 and 6-26 stand rejected. New claim 27 is supported throughout the application as filed, including at page

II. Patentability Arguments

A. The Claims Are Novel Over Davis

The Examiner maintained the rejection of claims 1-4, 8, 9, 12, 23, and 26 under 35 U.S.C. § 102(b) over Davis, asserting that the reference discloses the use of acetic acid or acetate alone as an elicitor. Office Action at pages 2-3. The Examiner further asserted that Davis discloses a method for eliciting antimicrobial phytoalexin compounds from soybean plants wherein the method comprises contacting living plants or cotyledons with an acetic acid buffer in amounts (e.g., about 0.1%, 0.08% or 12 mM and more; Fig. 6) effective to elicit and to recover phytoalexins into the aqueous medium. *Id.* at 3. In response, the Applicants respectfully disagree with the Examiner's position.

The Examiner relied on Fig. 6 of Davis for a disclosure of an effective amount of an acetic acid buffer being used to elicit phytoalexins from soybean cotyledons. However, Davis specifically states that "acetate is not acting as a general promoter of phytoalexin accumulation" (emphasis added; *see* p. 30, left column, lines 12-16). Therefore, acetate is not acting as an elicitor of phytoalexins, as the Examiner asserts, and Davis is actually teaching away from the present invention. Moreover, Fig. 6 of Davis does not show data

relating to an "acetic acid" buffer; rather, the data relate to the use of a "sodium acetate/bicarbonate buffer" with a molar ratio of 4:3 (*see* legend to Fig. 6 of Davis). Davis presents Fig. 6 to show the "[e]ffect of sodium acetate on the elicitor activity of hexa-β-glucosyl glucitol." (*Id.*) Importantly, Davis expressly states in that legend that "since . . . bicarbonate was not necessary for promotion of the elicitor activity of the hexa-β-glucosyl glucitol . . ., only the sodium acetate concentration is shown in the figure." (*Id.*) Thus, the control graph of Fig. 6 (open symbols) illustrates **the effect of different concentrations of the sodium acetate/bicarbonate buffer** on the cotyledons exposed to 10 ng/ml solution of hexa-β-glucosyl glucitol, **not the effect of different concentrations of acetic acid**. While the legend explains that the bicarbonate component of the buffer had no effect on the hexa-β-glucosyl glucitol elicitor activity, and for that reason Fig. 6 only shows the concentration of sodium acetate in the buffer, that shorthand reference to the buffer is only relevant to effects on hexa-β-glucosyl glucitol elicitor activity. Moreover, the legend clarifies that an acetate/bicarbonate buffer was used to generate the results shown in Fig. 6. Neither the figure nor its legend attributes any elicitor activity directly to sodium acetate or bicarbonate. To the extent that the Examiner persists in asserting that the buffer described in the legend to Fig. 6 of Davis exhibits elicitor activity, notwithstanding the essentially flat slope of the relevant curve (see below), reconciliation of the above-quoted statement from Davis that acetate does not generally promote (i.e., elicit) phytoalexins with the data of Fig. 6 would lead one of skill in the art to conclude that the bicarbonate is responsible for any elicitor activity seen in the control curve of Fig. 6, and <u>not</u> the acetate component. Thus, if Davis is teaching an elicitor activity for the acetate/bicarbonate buffer of Fig. 6, Davis is teaching away from the claimed invention.

In addition, Fig. 6 uses multiple filled symbols and open symbols without adequate identification. Further, no significance is attached to the relatively modest slope of the curve identified in Davis as a control curve relative to the curve identified in Davis as demonstrating the elicitor activity of hexa-β-glucosyl glucitol. Thus, the modest slope of the control curve may be within the range of error as no tests for significance have been provided. Thus, Davis does not provide an enabling teaching that would lead one of skill to the use of any buffer component disclosed in Fig. 6.

Consistent with the preceding clarification of the data disclosed in Fig. 6, the abstract of Davis identifies "specific elicitors" in the form of "hexa-β-glucosyl glucitol," "endopolygalacturonic acid lyase," and "oligogalacturonides" as inducing soybean cotyledons

to accumulate phytoalexins. The abstract continues, noting that "the elicitor-active hexa-β-glucosyl glucitol acts synergistically with several biotic and abiotic elicitors in the induction of phytoalexins in soybean cotyledons." In contrast, the abstract subsequently identifies dilute solutions of cell-damaging buffers, including sodium acetate buffers. These "buffers" are identified as a class of compounds distinct from the "specific elicitors," the "biotic elicitors," and the "abiotic elicitors" referenced earlier in the abstract. The "specific elicitors" are expressly identified in the abstract of Davis, as noted above, while Davis states that "[a]biotic elicitors include detergents and heavy metal salts, such as $HgCl_2$" (pages 23-24) and "[b]iotic elicitors include a variety of compounds isolated from microorganisms and plant tissues" (page 24). Moreover, in a section of the reference entitled "*Sources of phytoalexin elicitors*," Davis describes the sources of hexa-β-glucosyl glucitol, sodium polypectate fragments, and high molecular weight glucans, but not sodium acetate, or acetic acid. *See* pages 24-25. Thus, Davis itself is not identifying acetate compounds as elicitors, but rather as buffers.

Further confirmation that Davis is not disclosing acetate, or acetic acid, as an elicitor of therapeutics in plants is found in the Results section of the paper. Davis states that "the stimulation of elicitor activity by sodium acetate was specific for the hexa-β-glucosyl glucitol; sodium acetate did not stimulate the elicitor activity of either PGA lyase or the decagalacturonide (data not shown)." Davis, page 28. If sodium acetate itself were an elicitor, one would expect it to be active in the presence of any of the aforementioned compounds. Thus, Davis itself recognized that sodium acetate was not an elicitor.

Davis then addresses the potential effect that acetic acid might have on plant cells by noting that "[s]everal studies have demonstrated that certain organic acids, including acetic acid, are toxic to plant cells (8, 27, 33). We suggest that the increased elicitor activity of the hexa-β-glucosyl glucitol assayed in the presence of sodium acetate is due to cell damage and the subsequent release of a factor (perhaps an oligogalacturonide) that acts synergistically with the hexa-β-glucosyl glucitol in the induction of phytoalexin accumulation." Page 28. Consistently, Davis also states that "[t]his suggests that the ability of sodium acetate to enhance the induction of phytoalexins by the hexa-β-glucosyl glucitol may be due to cell damage caused by sodium acetate and subsequent release of oligogalacturonides that act synergistically with the hexa-β-glucosyl glucitol." Page 29. Davis further proposes that the released "oligogalacturonides act as signals of tissue damage" and "enhance the response of plant tissues to the elicitor-active molecules." Davis, abstract.

The express statements in Davis establish that the Davis reference did not disclose, expressly or inherently, that acetate (or acetic acid) was an elicitor of any compound in a plant. Rather, acetate, in a sodium acetate/bicarbonate buffer, was apparently an enhancer of a particular elicitor, hexa-β-glucosyl glucitol, and it was the latter compound that induced phytoalexins in soybean cotyledons. The enhancing effect was ascribed to acetate damaging or killing plant cells, thereby releasing a compound that interacted with hexa-β-glucosyl glucitol in eliciting phytoalexin production in soybeans. Consequently, Davis does not disclose, expressly or inherently, the contacting of a living intact plant or plant part with an amount of acetic acid effective to induce the production of a compound from the plant or plant part.

Davis also fails to disclose an "intact plant or plant part" being contacted with an elicitor. Cells in culture, as Davis used, are undifferentiated and are completely different from an intact plant or plant part, which are differentiated. In the section titled "*Assay for elicitor activity*," the Davis reference expressly states that "[a] 90-µl aliquot of the test solutions [containing candidate elicitors] was applied to the wounded surface of each of twenty cotyledons per trial." Davis, page 25; emphasis added. Davis further describes the assay as involving the spectrophotometric measurement of absorbance at A_{286} of "wound droplet solutions" relative to maximal absorption at A_{286} using the strongest known elicitor of phytoalexin. *Id.* That relative measurement is a measure of A_{286}/A_{286max}, as explained at page 25 of Davis. The elicitor activity reported in Fig. 6 on page 29 of Davis, upon which the Examiner has relied, was determined by measuring A_{286}/A_{286max}. Thus, the Examiner is relying on the disclosure of experimental results relating to an undifferentiated plant part (soybean cotyledon) that is not intact (it is wounded). Davis, therefore, fails to disclose an element of the claims in failing to disclose an "intact plant or plant part" being contacted with any compound, such as acetic acid. The Applicants submit that "intact" modifies both plant and plant part. Therefore, Davis does not anticipate the differentiated and intact plant or plant part of the present invention.

Further, Davis addresses the production of phytoalexins in soybeans and discloses that the accumulation of those phytoalexins is measured spectrophotometrically (i.e., through absorbance readings and ratios thereof). Nowhere does Davis disclose, expressly or inherently, the recovery of those phytoalexins. In explaining the effect of sodium acetate on plant cells, Davis acknowledges that acetate may damage plant cells, thereby releasing a factor, perhaps an oligogalacturonide, that acts synergistically with hexa-β-glucosyl glucitol

in eliciting phytoalexins from soybean. It is that factor that is released by exposure to acetate, not the product (phytoalexin) being elicited by hexa-β-glucosyl glucitol. One of skill would not expect a plant cell damaged to the point of releasing such a factor to be capable of producing or accumulating an elicited compound such as phytoalexin. Thus, Davis does not disclose the "release" of phytoalexins as maintained by the Examiner. Davis does not indicate that the phytoalexins being measured spectrophotometrically were extracellular rather than intracellular. Accordingly, Davis fails to disclose an element of the claims in failing to disclose the recovery of the produced compound from an intact plant or plant part.

In addition, the Applicants disagree with the Examiner's assumption that 0.1% sodium acetate is the same as 0.1% acetic acid. It is well known in the art that acetic acid is a weak organic acid with an acid dissociation constant K of 1.85×10^{-5} (*see* University Chemistry, Third Ed., pp. 220-226 (attached as Appendix A to the response filed June 17, 2004). The acid dissociation constant is a measure of acid strength and, for acetic acid, is determined as follows: $K = ([H_3O^+][\text{acetate anion}])/[\text{acetic acid}]$, where the square brackets indicate concentrations. Thus, the acid dissociation constant for acetic acid is $K = 1.85 \times 10^{-5} = ([H_3O^+][\text{acetate anion}])/[\text{acetic acid}]$. The product of the ion concentrations of dissociated acetic acid is much less than the concentration of undissociated acetic acid, consistent with the recognition of that acid as a weak acid. Further, when considering an acetate salt such as sodium acetate, one must also consider the influence of the paired ion (e.g., sodium) on the equilibrium position. The conversion of sodium acetate to acetic acid involves the concomitant formation of NaOH, a very strong base. As a very strong base, NaOH is almost completely dissociated under most conditions. The presence of the sodium and hydroxide ions affects the equilibrium position of sodium acetate and acetic acid, shifting the equilibrium position towards sodium acetate. Therefore, very little sodium acetate is converted to acetic acid because of the necessary co-production of NaOH, which strongly tends to dissociate. Accordingly, it is scientifically unreasonable to assert that 0.1% sodium acetate is the same as 0.1% acetic acid.

Finally, the Applicants submit that Davis does not teach the use of acetate buffer alone as an elicitor, as the Examiner contends. Office Action at page 7. Although Davis shows the concentration of sodium acetate only in Figure 6, sodium acetate was always used in conjunction with bicarbonate in a mixed buffer solution to perform the various experiments. Davis did not look at the effect of acetate alone as an elicitor. Therefore, Davis did not disclose the sole use of acetate buffer as an elicitor.

For all of the foregoing reasons, the Applicants respectfully submit that Davis is defective in not disclosing, expressly or inherently, each element of any one of the presently pending claims. At a minimum, (1) Davis specifically states that "acetate is not acting as a general promoter of phytoalexin accumulation" (*see* p. 30, left column, lines 12-16), (2) Fig. 6 of Davis does not disclose that sodium acetate is an elicitor of phytoalexins in soybean cotyledons, (3) Davis does not disclose the recovery of any elicited product, and (4) neither Davis nor the art discloses that sodium acetate and acetic acid can be quantitatively interconverted. Accordingly, the Office has failed to establish a *prima facie* case of anticipation for any of the pending claims under 35 U.S.C. § 102(b) over Davis and the rejection should be withdrawn.

B. The Claims Are Non-obvious Over Davis in View of Secondary References

The Examiner rejected claims 1-4 and 6-26 under 35 U.S.C. § 103(a) over Davis, in view of Stevens and further in view of Jurd and/or Yamazaki. In support, the Examiner relied on Davis for the proposition established above in addressing the novelty of the pending claims (i.e., "the use of acetic acid as a plant elicitor"). Office Action at pages 3-4. The secondary references were relied on for disclosures that 1) therapeutic flavonoids may be extracted from leaf cuticle (Stevens); 2) flavonoids have antimicrobial activity (Jurd); and 3) maceration is used to elicit and recover therapeutically active compounds from plant parts (Yamazaki). Office Action at pages 4-6. The Applicants respectfully traverse the rejection.

The Examiner's reliance on Davis as the primary reference is misplaced because (1) Davis specifically states that "acetate is not acting as a general promoter of phytoalexin accumulation" (*see* p. 30, left column, lines 12-16), (2) Fig. 6 of Davis does not disclose that sodium acetate is an elicitor of phytoalexins in soybean cotyledons, (3) Davis does not disclose the recovery of any elicited product, and (4) neither Davis nor the art discloses that sodium acetate and acetic acid can be quantitatively interconverted. The secondary reference, Stevens, that was cited by the Examiner against claims 1-4, 8-9, 12, 23, and 26, does not remedy any of the deficiencies of Davis.

Stevens is cited for the proposition that flavonoid anti-microbials can be extracted from plants to provide a chemical library of chemical therapeutics. Office Action at pages 4-5. Stevens does not disclose or suggest the use of an elicitor, such as the acetic acid recited in

the pending claims. Stevens does not take issue with the settled principle that an acid and its component ions achieve an equilibrium state characterized by the acid dissociation constant (i.e., $K = ([H^+][anion])/[acid]$, for protic acids). Accordingly, Stevens does not disclose or suggest that sodium acetate can be quantitatively converted to acetic acid. Moreover, there is no motivation to combine Davis and Stevens. Davis teaches sodium acetate as a cell-damaging buffer that may release a compound that acts synergistically with hexa-β-glucosyl glucitol in eliciting the production of phytoalexins in soybean. Even if one were to misconstrue the remainder of the disclosure of Davis and accept that Davis teaches the use of acetic acid as a plant elicitor, one would not look to Stevens for a method of recovering an elicited product because Stevens does not teach the recovery of any product from plant cells damaged in the course of eliciting production of a compound. Accordingly, the Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness for the claimed subject matter in view of Davis and Stevens. Accordingly, the rejection of claims 1-4, 8-9, 12, 23, and 26 under § 103(a) over Davis in view of Stevens has been overcome.

The Examiner rejected claims 1-4, 7-21, 23, and 25-26 under § 103(a) over Davis in view of Stevens and Jurd. Reliance was placed on Jurd as teaching assays of therapeutically active anti-microbial flavonoids by using culture turbidity or cell counts as a measure of cell viability. Again, Jurd does not remedy any of the above-noted deficiencies in the disclosure of Davis, and the Examiner has not maintained otherwise. Jurd does not disclose or suggest the use of sodium acetate, or acetic acid, as an elicitor of therapeutic compounds in intact plants or plant parts. Nor does Jurd disclose or suggest the quantitative interconversion of sodium acetate and acetic acid. Further, as for the asserted combination of Davis and Stevens, there is no proper motivation for combining Davis and Jurd. Jurd does not disclose or suggest a method of recovering a therapeutic compound from a plant cell following exposure of that cell to a cell-damaging agent such as acetic acid or sodium acetate. Accordingly, one would not look to Jurd for a method of recovering products produced using a method of eliciting erroneously attributed to the disclosure of Davis. Thus, the Office has failed to establish a *prima facie* case of obviousness for the claimed subject matter in view of Davis and Jurd. Accordingly, the rejection of claims 1-4, 8-9, 12, 22-23, and 26 under § 103(a) over Davis in view of Jurd has been overcome.

The Examiner rejected claims 1-4 and 6-26 under § 103(a) over Davis in view of Stevens, Jurd and Yamazaki, with Yamazaki being cited as teaching the maceration of plant materials to recover products found within such materials. Regardless of the accuracy of that characterization of Yamazaki, the Yamazaki reference does not remedy the deficiencies in the Davis disclosure noted above. Yamazaki does not disclose or suggest the use of sodium acetate, or acetic acid, as an elicitor of a therapeutic compound in an intact plant or plant part, and Yamazaki does not disclose or suggest the quantitative interconversion of sodium acetate and acetic acid under any set of conditions. Accordingly, Yamazaki, like Stevens and Jurd, does not remedy the deficiencies in the disclosure of Davis noted above, and the Examiner has not maintained otherwise. Therefore, the Office has not established a *prima facie* case of obviousness for the claimed subject matter in view of Davis and Yamazaki, and the rejection of claims 1-4 and 6-26 under § 103(a) over Davis in view of Yamazaki has been overcome.

For all of the foregoing reasons, the Applicants respectfully submit that the rejection of claims 1-4, and 6-26 under 35 U.S.C. § 103(a) over Davis in view of any of Stevens, Jurd, and/orYamazaki should be withdrawn.

VI. CONCLUSION

In view of the remarks made herein, the Applicants respectfully submit that claims 1-4 and 6-26 are in condition for allowance and respectfully request expedited notification thereof.

Respectfully submitted,
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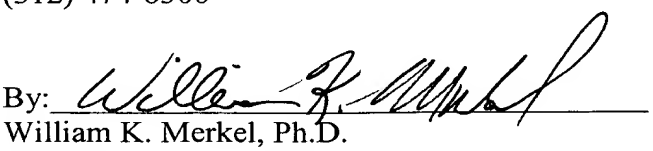
By: 
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